UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,376	10/19/2005	Ken Inose	TOYA114.011APC	6992

20995 7590 06/04/2009

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
06/04/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/553,376	INOSE ET AL.	
	Examiner	Art Unit	
	ANGELA BERTAGNA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Applications

1. Applicant's response filed on March 26, 2009 is acknowledged. Claims 1-5, 9, and 10 are currently pending. In the response, Applicant amended claim 1.

The following are new grounds of rejection necessitated by Applicant's amendments to the claims. Any previously made rejections not reiterated below have been withdrawn in view of the amendment. Applicant's arguments filed on March 26, 2009 that remain relevant to the new grounds of rejection have been fully considered, but they were not persuasive for the reasons set forth in below. Accordingly, this Office Action is made **FINAL**.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 3, 4, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lurquin et al. (Analytical Biochemistry (1975) 65: 1-10; cited previously) in view of Vosbeck et al. (The Journal of Biological Chemistry (1973) 248(17): 6029-6034; cited previously) and further in view of Werner et al. (Plant Molecular Biology Reporter (1998) 16: 295-299; newly cited).

These claims are drawn to a method for isolating nucleic acids from a sample comprising eukaryotic cells and amplifying the isolated nucleic acids by PCR. The method comprises dissolving the sample in a buffer comprising a surfactant and a salt of a monovalent cation, heating the resulting solution at 80-100°C, performing gel filtration to obtain a solution containing nucleic acids, and amplifying a target DNA in the solution by PCR.

Lurquin teaches a method for isolating nucleic acids from eukaryotic cells (see abstract and page 3).

Regarding claims 1, 3, 9, and 10, the method of Lurquin comprises the following steps: (see page 3, 1st paragraph of the "Results and Discussion" section):

(a) dissolving a sample in a buffer comprising at least one surfactant and at least one salt of a monovalent cation (*i.e.* the saline-EDTA buffer comprising sodium sarcosylate),

(b) heating the obtained solution at 37°C,

(c) adding additional NaCl to a final concentration of 2M,

(d) removing PCR inhibitory substances by subjecting the heated solution to gel filtration, and

(e) collecting a solution fraction containing nucleic acids.

Regarding claim 4, the *Chlamydomonas reinhardi* cells used in the method of Lurquin are eukaryotic cells.

Lurquin does not teach heating the solution at a temperature within the claimed ranges of 80-100°C, 90-100°C, and 95-100°C. Also, Lurquin teaches adding NaCl to a final concentration of 2M after the heating step rather than before the heating step as required by claim 1.

Vosbeck studied the properties of the mixture of enzymes known as pronase (see abstract). Regarding claims 1, 9, and 10, Vosbeck teaches that pronase activity is eliminated at high temperatures, specifically temperatures above 80°C (see Figure 8).

Neither Lurquin nor Vosbeck teaches PCR amplification of isolated nucleic acids.

Werner teaches a PCR-based method for determining the mating type of *Chlamydomonas reinhardi* (see abstract and pages 296-297). The method of Werner comprises isolating DNA from *Chlamydomonas reinhardi* and amplifying the isolated DNA by PCR (pages 296-297).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to add NaCl to a final concentration of 2M to the saline/EDTA/surfactant buffer used in the method of Lurquin before conducting the heating step. As noted in MPEP 2144.04 IV C, the selection of any order of mixing ingredients is *prima facie* obvious in the absence of unexpected results. In this case, there is no particular reason for adding the sodium chloride before or after the heating step, and therefore, in the absence of unexpected results, the claimed order of addition is *prima facie* obvious. Also, it would have been obvious for one of ordinary skill in the art at the time of invention to include a high temperature heating step in the method of Lurquin. An ordinary artisan would have been motivated to do so in order to ensure pronase inactivation. An ordinary artisan would have been particularly motivated to use a temperature

within the claimed ranges, since Vosbeck taught that pronase was inactivated at 90°C (Figure 8). Finally, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to amplify the DNA isolated by the method resulting from the combined teachings of Lurquin and Vosbeck by PCR. An ordinary artisan would have been motivated to do so with a reasonable expectation of success, since Werner taught that this was a rapid, simple, and reliable method for determining the mating type of a *Chlamydomonas reinhardi* strain (see abstract and pages 296-297). Thus, the methods of claims 1, 3, 4, 9, and 10 are *prima facie* obvious over Lurquin in view of Vosbeck and further in view of Werner in the absence of unexpected results.

Response to Arguments:

Applicant's arguments filed on March 26, 2009 have been fully considered, but they were not persuasive.

Applicant first argues that the combined teachings of Lurquin and Vosbeck do suggest the new limitation requiring PCR amplification of an object DNA isolated using the claimed method (see page 3). This argument is moot in view of the new grounds of rejection above, where the newly cited Werner reference suggests amplifying DNA isolated by the method resulting from the combined teachings of Lurquin and Vosbeck using PCR.

Applicant also argues that that adding the salt of a monovalent cation at a concentration of 0.5 - 2.0 M before conducting the heating step is critical for dissociating histones, which are electrostatically bound to DNA and inhibit polymerase-mediated DNA amplification (see pages 3-4). This argument was not persuasive, because as discussed above, the teachings of Vosbeck would have suggested to the ordinary artisan that including a high-temperature pronase

inactivation step in the method of Lurquin would provide the benefit of eliminating undesirable residual pronase activity. It would have been *prima facie* obvious for the ordinary artisan to conduct the high temperature pronase inactivation step suggested by Vosbeck at any point in the method disclosed by Lurquin following the 1 hour incubation with pronase at 37°C (*e.g.*, after the addition of the high salt solution and before the gel filtration step). In this embodiment suggested by the combined teachings of Lurquin and Vosbeck, the high temperature incubation step occurs after the salt addition step. It is also noted that the pronase digestion step taught by Lurquin would inherently result in the degradation of DNA-associated histones, and therefore, the method resulting from the combined teachings of Lurquin and Vosbeck would not appear to produce the aggregates described by Applicant as rendering the method unsuitable for subsequent PCR amplification. Since Applicant's arguments were not persuasive, the rejection has been maintained with modifications to account for the newly added limitations.

4. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lurquin et al. (Analytical Biochemistry (1975) 65: 1-10; cited previously) in view of Vosbeck et al. (The Journal of Biological Chemistry (1973) 248(17): 6029-6034; cited previously) and further in view of Werner et al. (Plant Molecular Biology Reporter (1998) 16: 295-299; newly cited) and further in view of Wilson et al. (US 7,045,679 B1; cited previously).

Claim 2 is drawn to the method of claim 1, wherein the surfactant is Triton X-100.

The combined teachings of Lurquin, Vosbeck, and Werner result in the method of claims 1, 3, 4, 9, and 10, as discussed above.

Lurquin teaches that the surfactant is sodium sarcosylate rather than Triton X-100 (see page 3, 1st paragraph of the "Results and Discussion" section).

Wilson teaches a method for isolating nucleic acids from plant cells (see Example 1 at column 7).

Regarding claim 2, Wilson teaches the use of Triton X-100 in the lysis buffer (column 7, lines 16-19).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute Triton X-100 for sodium sarcosylate when practicing the method resulting from the combined teachings of Lurquin, Vosbeck, and Werner. Since Wilson taught that Triton X-100 could be used as the surfactant in a lysis buffer used in a method of isolating nucleic acids from plant cells, an ordinary artisan would have recognized that Triton X-100 and sodium sarcosylate were art-recognized equivalents useful for the same purpose, and therefore, would have been motivated to substitute one for the other with a reasonable expectation of success. As noted in MPEP 2144.06 II, the substitution of art-recognized equivalents known to be useful for the same purpose is *prima facie* obvious in the absence of secondary considerations. Thus, the method of claim 2 is *prima facie* obvious in view of the combined teachings of the cited references in the absence of unexpected results.

Response to Arguments

Applicant argues that the rejection should be withdrawn, since the primary combination of references (Lurquin and Vosbeck) does not teach or suggest all of the limitations of independent claim 1 from which claim 2 depends (page 4). This argument was not persuasive,

because as discussed above, the new grounds of rejection made above citing Lurquin, Vosbeck, and Werner suggest the method of independent claim 1.

5. Claims 1-5, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burdick et al. (EP 0 393 744 A1; cited previously) in view of Akane et al. (Biotechniques (1994) 16(2): 235, 237, 238; cited previously).

These claims are drawn to a method for isolating nucleic acids from a sample comprising eukaryotic cells, specifically a blood sample. The method comprises dissolving the sample in a buffer comprising a surfactant and a salt of a monovalent cation, heating the resulting solution at 80-100°C, and performing gel filtration to obtain a solution containing nucleic acids.

Burdick teaches methods for isolating nucleic acids from whole blood or peripheral blood mononuclear cells (see abstract and Example 2 at column 14, lines 26-44).

Regarding claims 1, 9, and 10, the method of Burdick comprises:

(a) dissolving a sample in a buffer comprising at least one surfactant and at least one salt of a monovalent cation (column 14, lines 32-39)

(b) heating the obtained solution at 80-100°C (column 14, lines 39-41 teaches heating at 118°C; column 6, lines 33-37 teach heating at 80-120°C or 95-120°C; column 6, lines 16-19 teach heating at 100°C)

(c) filtering the heated solution (column 6, lines 52-57 and column 14, lines 41-42)

(d) collecting a solution fraction containing nucleic acids (column 6, lines 52-57 and column 14, lines 41-42)

(e) amplifying an object DNA from the fraction containing nucleic acids by PCR (column 14, line 40 – column 15, line 3).

Regarding claim 2, Burdick teaches that the surfactant is Triton X-100 (column 14, lines 37-38).

Regarding claim 3, Burdick teaches that the salt is NaCl (column 14, lines 38-39).

Regarding claims 4 and 5, Burdick teaches that the sample is a blood sample that comprises eukaryotic cells (column 14, lines 25-35).

Burdick teaches filtering the heated solution through a membrane filter (column 6, lines 52-57 and column 14, lines 41-42), but does not teach conducting a gel filtration step as required by claim 1. Also, Burdick teaches using NaCl at a concentration of 0.5 to 1.5 weight percent (86 mM – 257 mM), rather than a value within the claimed concentration range of 0.5 - 2 M.

Akane teaches methods of preparing DNA samples for PCR comprising a gel filtration step (page 235). Regarding claim 1, Akane teaches that degraded DNA and a hemoglobin derivative (hematin) isolated from forensic samples interfere with PCR amplification (page 235, column 2). Akane further teaches that although contaminating hematin may be removed by treatment with bovine serum albumin, ultrafiltration, chelating resin treatment, gel filtration or anion-exchange chromatography, degraded DNA may only be removed using gel filtration (page 235, column 2).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to incorporate a gel filtration step into the nucleic acid purification method taught by Burdick. Since the method of Burdick comprised a PCR amplification step following nucleic acid isolation (column 14, lines 41-44), an ordinary artisan would have been motivated to

incorporate a gel filtration step, as suggested by Akane, in order to remove any contaminating degraded DNA fragments that would interfere with the PCR. An ordinary artisan would have had a reasonable expectation of success in incorporating a gel filtration step into the method of Burdick since both methods were directed to purification of DNA from forensic samples for PCR analysis.

It also would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to optimize the NaCl concentration when practicing the nucleic acid isolation method resulting from the combined teachings of Burdick and Akane. An ordinary artisan would have been motivated to optimize this results-effective variable in order to improve salt-induced precipitation of contaminating proteins present in the sample prior to the filtration step. As noted in MPEP 2144.05, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. '[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.' *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (MPEP 2144.05)." Routine optimization is not inventive and there is no evidence to suggest that the selection of the claimed salt concentrations was other than routine or that the results should be considered unexpected compared to the closest prior art. Thus, the methods of claims 1-5, 9, and 10 are *prima facie* obvious over Burdick in view of Akane in the absence of secondary considerations.

Response to Arguments:

Applicant's arguments filed on March 26, 2009 have been fully considered, but they were not persuasive.

Applicant first argues that one of ordinary skill in the art would not have been motivated to increase the salt concentration when practicing the method resulting from the combined teachings of Burdick and Akane, because high salt concentrations were known in the art to inhibit the activity of DNA polymerase (see page 5). Applicant also argues that one of ordinary skill in the art would not have been motivated to obviate this problem by diluting the sample, since doing so would also reduce the amount of DNA present in the sample, thereby compromising the sensitivity of any subsequently performed PCR assays (see page 5). Applicant further argues that the claimed salt concentrations are critical for practice of the claimed method and reiterates the arguments filed on September 15, 2008 (see page 5).

Applicant's first and second arguments were not persuasive, because as discussed previously, an ordinary artisan would have be motivated to perform routine optimization to optimize results-effective variables, such as the dilution factor, when practicing the method resulting from the combined teachings of Burdick and Akane. Since Burdick expressly taught diluting the isolated nucleic acids prior to amplification, and since dilution factors, such as 50-fold or 25-fold, were routinely used in PCR amplification, an ordinary artisan would have had a reasonable expectation of success in practicing the method suggested by the combined teachings of Burdick and Akane. It is also noted that obviousness only requires a *reasonable* expectation of success (MPEP 2143.02 I). In this, case an ordinary artisan would have recognized from the prior art (*e.g.* the Chien reference cited by Applicant), that obtaining PCR amplifiable nucleic

acids required a low levels of monovalent salts, such as NaCl, and therefore, would have been motivated to optimize the approximately 10-fold dilution factor taught by Burdick (*e.g.* to factors such as 25-fold or 50-fold) as necessary when optimizing the salt concentration to provide maximal lysis and protein precipitation in the method of Burdick. In other words, since Burdick expressly teaches dilution of the isolated nucleic acids prior to conducting PCR amplification, the reference clearly accounts for the issues raised in Applicant's arguments concerning residual salt and sensitivity of subsequent PCR amplification reactions, and therefore, does not teach away from or preclude a reasonable expectation of success in optimizing the salt concentration and the dilution factor as discussed above.

Applicant's third argument was also unpersuasive, because as discussed previously, Applicant's arguments regarding the criticality of the range are not commensurate in scope with the claims. Applicant's arguments and the cited non-patent literature references are directed to the issue of disrupting protein-DNA interactions for subsequent use in PCR amplification methods (see pages 5-6). However, the claimed methods do not require that the isolated nucleic acids obtained after the gel filtration step are free of all associated proteins. Also, the claimed methods are not limited to DNA isolation, but encompass RNA purification and amplification by RT-PCR. Furthermore, the claimed methods are not limited to eukaryotic systems in which histones must be separated from genomic DNA to be amplified. As a result, the claimed salt concentrations do not appear to be critical to practice of the invention. Also, even if some of the genomic DNA obtained from the blood samples of Burdick and Akane is still associated with proteins, this would not necessarily preclude practice of the method resulting from the combined teachings of Burdick and Akane, since Burdick emphasizes using the method to isolate and

detect viral nucleic acids (see column 5), which do not exist in the blood cells in the form of chromatin. Since Applicant's arguments were not found persuasive, the rejection of claims 1-5, 9, and 10 under 35 U.S.C. 103(a) as being unpatentable over Burdick in view of Akane has been maintained.

Conclusion

6. No claims are currently allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

amb

/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637